CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-153/21-154

CHEMISTRY REVIEW(S)

Review of Chemistry, Manufacturing, and Controls

1.NDA:# 21-153 2. CHEM REVIEW # 4 3.REVIEW DATE: 02-Jan-2001
4.APPLICATION HISTORY

SUBMISSIONS REVIEWED

DOCUMENT CDER ASSIGNED

Amendment BC

20-Dec-2000 22-Dec-2000 29-Dec-2000

PREVIOUS DOCUMENTS:

| DOCUMENT | DOCUMENT DATE |
|--|---------------|
| Original | 03-Dec-1999 |
| Amendment AZ | 03-Apr-2000 |
| Amendment BC | 01-Jun-2000 |
| Amendment BC | 23-Jun-2000 |
| Amendment BC | 17-Jul-2000 |
| Amendment BL | 02-Aug-2000 |
| Amendment BC | 25-Aug-2000 |
| Chem. Review #1 | 22-Sep-2000 |
| DR Letter | 30-Sep-2000 |
| AE Letter | 03-Oct-2000 |
| OPDRA Review of October 16 amendment | 24-Oct-2000 |
| IR Letter | 15-Nov-2000 |
| Amendment BZ | 06-Oct-2000 |
| Amendment BC | 13-Oct-2000 |
| Amendment AL, MR | 16-Oct-2000 |
| OPDRA Review of October 16 amendment | 24-Oct-2000 |
| IR Letter | 15-Nov-2000 |
| Amendment BC | 19-Oct-2000 |
| Chem. Review #2 | 28-Nov-2000 |
| DR Letter | 29-Nov-2000 |
| BL Amendment | 20-Nov-2000 |
| Chem. Review #3 (Review of BL Amendment only | 07-Dec-2000 |

5. NAME & ADDRESS OF APPLICANT:

AstraZeneca LP

1800 Concord Pike

P.O. Box 8355

Wilmington DE 19803-8355

6. DRUG PRODUCT NAME:

Proprietary: Nexium

Nonproprietary/USAN: esomeprazole magnesium

Chem. Type/Ther. Class: 1S

Code names: H 199/18

7. PHARMACOLOGICAL CATEGORY: proton pump inhibitor

8. INDICATION: acute healing of erosive esophagitis,

maintenance of healing of erosive esophagitis, and treatment

of symptomatic gastroesophageal reflux disease (sGERD)

9. DOSAGE FORM: delayed release pellets

10. STRENGTH: — 20, and 40 mg. Approval only for 20 and 40 mg strengths

11. ROUTE OF ADMINISTRATION: oral

12. HOW DISPENSED: X RX OTC

13. CHEMICAL IDENTIFICATION:

N Bis (1H-Benzimidazole,5-methoxy-2-[(S)-[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl]-),magnesium salt, trihydrate

 $(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O.$

CAS Number 217087-09-7

MW= 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)

- 14. SUPPORTING DOCUMENTS:
- 15. RELATED DOCUMENTS NDA 19-810
- 16. CONSULTS: Biometrics and Biopharm complete
- 17. REMARKS/COMMENTS: The MV package needs updating. Send DR Letter. Specifications for ______ should be amended.
- 18. CONCLUSIONS & RECOMMENDATIONS: Approvable

Arthur B. Shaw, Ph.D. Review Chemist HFD-180

Liang Zhou, Ph.D. Chemistry Team Leader, HFD-180

cc:

NDA 21-153

HFD-180/Division File/NDA 21-153

HFD-181/CSO

HFD-180/LTalarico

HFD-180/LZhou

HFD-180/HGallo-Torres

HFD-180/AShaw

R/D Init by: 09-Jan-2001

f/t/ABS 09-Jan-2001

Art Shaw 1/9/01 05:48:33 PM CHEMIST

Liang Zhou 1/10/01 12:30:38 PM CHEMIST

APPEARS THIS WAY ON ORIGINAL

Review of Chemistry, Manufacturing, and Controls

1. NDA: # 21-153 2. CHEM REVIEW # 3 3. REVIEW DATE: 06-Dec-2000

4. APPLICATION HISTORY

SUBMISSIONS REVIEWED

 DOCUMENT
 CDER
 ASSIGNED

 20-Nov-2000
 21-Nov-2000
 28-Nov-2000

PREVIOUS DOCUMENTS:

Amendment BL

| PREVIOUS DOCUMENTS: | |
|--------------------------------------|---------------|
| DOCUMENT | DOCUMENT DATE |
| Original | 03-Dec-1999 |
| Amendment AZ | 03-Apr-2000 |
| Amendment BC | 01-Jun-2000 |
| Amendment BC | 23-Jun-2000 |
| Amendment BC | 17-Jul-2000 |
| Amendment BL | 02-Aug-2000 |
| Amendment BC | 25-Aug-2000 |
| Chem. Review #1 | 22-Sep-2000 |
| DR Letter | 30-Sep-2000 |
| AE Letter | 03-Oct-2000 |
| OPDRA Review of October 16 amendment | 24-Oct-2000 |
| IR Letter | 15-Nov-2000 |
| Amendment BZ | 06-Oct-2000 |
| Amendment BC | 13-Oct-2000 |
| Amendment AL, MR | 16-Oct-2000 |
| Amendment BC | 19-Oct-2000 |
| Chem. Review #2 | 28-Nov-2000 |
| DR Letter | 28-Nov-2000 |

5. NAME & ADDRESS OF APPLICANT:

AstraZeneca LP

725 Chesterbrook Blvd Wayne PA 19087-5677

6. DRUG PRODUCT NAME:

Proprietary: Nexium

Nonproprietary/USAN: esomeprazole magnesium

Chem.Type/Ther.Class: 1S

Code names: H 199/18

- 7. PHARMACOLOGICAL CATEGORY: proton pump inhibitor
- 8. <u>INDICATION:</u> acute healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic gastroesophageal reflux disease (sGERD)
- 9. DOSAGE FORM: delayed release pellets
- 10. STRENGTH: 20, and 40 mg. Approval only for 20 and 40 mg strengths

- 11. ROUTE OF ADMINISTRATION: oral
- 12. HOW DISPENSED: X RX OTC

13. CHEMICAL IDENTIFICATION:

N Bis (1H-Benzimidazole,5-methoxy-2-[(S)-[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl]-),magnesium salt, trihydrate

 $(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O.$

CAS Number 217087-09-7

MW= 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)

- 14. SUPPORTING DOCUMENTS: N/A
- 15. RELATED DOCUMENTS NDA 19-810, IND
- 16. CONSULTS: Biometrics and Biopharm ACCEPTABLE
- 17. REMARKS/COMMENTS: Labeling changes The applicant has made commitments to change certain aspects of the labeling of the blister, carton and bottles at the next printing.

 ACCEPTABLE
- 18. CONCLUSIONS & RECOMMENDATIONS: The application may be approved from a CMC point of view with a 24 month expiration date for 20 and 40 mg capsules packaged in 100 and 1000 count bottles and Hospital Unit Dose blister packages.

Arthur B. Shaw, Ph.D. Review Chemist HFD-180

Liang Zhou, Ph.D. Chemistry Team Leader, HFD-180

cc:

NDA 21-153

HFD-180/Division File/NDA 21-153

HFD-181/CSO

HFD-180/LTalarico

HFD-180/LZhou

HFD-180/HGallo-Torres

HFD-180/AShaw

R/D Init by:LZhou 06-Dec-2000

f/t/ABS 06-Dec-2000

/s/

Art Shaw

12/7/00 01:09:13 PM

CHEMIST

Laebling changes will be made at next printing

Liang Zhou

12/7/00 01:13:57 PM

CHEMIST

APPEARS THIS WAY ON ORIGINAL

Review of Chemistry, Manufacturing, and Controls

1. NDA: # 21-153 2. CHEM REVIEW # 2 3. REVIEW DATE: 18-Oct-2000

4.APPLICATION HISTORY

SUBMISSIONS REVIEWED

| | | | DOCUMENT | CDER | ASSIGNED |
|-----------|-----|----|-------------|-------------|-------------|
| Amendment | BZ | | 06-Oct-2000 | 10-Oct-2000 | 11-Oct-2000 |
| Amendment | BC | | 13-Oct-2000 | 16-Oct-2000 | 17-Oct-2000 |
| Amendment | AL, | MR | 16-Oct-2000 | 17-Oct-2000 | 18-Oct-2000 |
| Amendment | BC | | 19-Oct-2000 | 20-Oct-2000 | 24-Oct-2000 |

PREVIOUS DOCUMENTS:

| DOCUMENT | DOCUMENT DATE |
|--------------------------------------|---------------|
| Original | 03-Dec-1999 |
| Amendment AZ | 03-Apr-2000 |
| Amendment BC | 01-Jun-2000 |
| Amendment BC | 23-Jun-2000 |
| Amendment BC | 17-Jul-2000 |
| Amendment BL | 02-Aug-2000 |
| Amendment BC | 25-Aug-2000 |
| Chem. Review #1 | 22-Sep-2000 |
| DR Letter | 30-Sep-2000 |
| AE Letter ' | 03-Oct-2000 |
| OPDRA Review of October 16 amendment | 24-Oct-2000 |
| IR Letter | 15-Nov-2000 |

5. NAME & ADDRESS OF APPLICANT:

AstraZeneca LP 725 Chesterbrook Blvd Wayne PA 19087-5677

6. DRUG PRODUCT NAME:

Code names: H 199/18

See discussion below concerning the nomenclature

- 7. PHARMACOLOGICAL CATEGORY: proton pump inhibitor
- 8. <u>INDICATION:</u> acute healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic gastroesophageal reflux disease (sGERD)
- 9. DOSAGE FORM: delayed release pellets
- 10. STRENGTH: 20, and 40 mg. Approval only for 20 and 40

mg strengths

11. ROUTE OF ADMINISTRATION: oral

12. HOW DISPENSED: X RX OTC

13. CHEMICAL IDENTIFICATION:

N Bis (1H-Benzimidazole, 5-methoxy-2-[(S)-[4-methoxy-3, 5-dimethyl-2-pyridinyl)methyl)sulfinyl]-), magnesium salt, trihydrate

 $(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O.$

CAS Number 217087-09-7

MW= 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)

- 14. SUPPORTING DOCUMENTS: All are Type III. See Container Closure Section
- 15. RELATED DOCUMENTS NDA 19-810
- 16. CONSULTS: Biometrics and Biopharm complete
- 17. REMARKS/COMMENTS: The application is approvable with a 24 month expiration date. However, there is some information that should be provided either in an amendment to the NDA or as a post-approval commitment. There are some labeling comments that need to be discussed further with OPDRA.
- 18. CONCLUSIONS & RECOMMENDATIONS: Approvable. The applicant should be sent a Discipline Review Letter.

Arthur B. Shaw, Ph.D.
Review Chemist HFD-180

APPEARS THIS WAY ON ORIGINAL Liang Zhou, Ph.D./
Chemistry Team Leader, HFD-180

Review of Chemistry, Manufacturing, and Controls

1. NDA:# 21-153 2. CHEM REVIEW # 1 3. REVIEW DATE: 20-Sep-2000

4. SUBMISSIONS REVIEWED

| | | DOCUMENT | CDER | ASSIGNED |
|-----------|----|-------------|-------------|-------------|
| Original | | 03-Dec-1999 | 06-Dec-1999 | 07-Dec-1999 |
| Amendment | ΑZ | 03-Apr-2000 | 03-Apr-2000 | 10-Apr-2000 |
| Amendment | BC | 01-Jun-2000 | 02-Jun-2000 | 09-Jun-2000 |
| Amendment | BC | 23-Jun-2000 | 26-Jun-2000 | 03-Jul-2000 |
| Amendment | BC | 17-Jul-2000 | 18-Jul-2000 | 20-Jul-2000 |
| Amendment | BL | 02-Aug-2000 | 03-Aug-2000 | 08-Aug-2000 |
| Amendment | BC | 25-Aug-2000 | 28-Aug-2000 | 29-Aug-2000 |

5. NAME & ADDRESS OF APPLICANT:

AstraZeneca LP 725 Chesterbrook Blvd Wayne PA 19087-5677

6. DRUG PRODUCT NAME:

Proprietary: Nexium
Nonproprietary/USAN: esomeprazole magnesium
Chem.Type/Ther.Class: 1S
Code names: H 199/18

There is some confusion in the application. Sometimes H199/18 refers to the S-enantiomer of omeprazole. (Description of Drug substance, Page 004-002-012 of original submission Vol. 1.6) Sometimes it refers to "esomeprazole magnesium" (Cover letter to original submission)

COMMENTO: The applicant should clarify the use of the name "H199/18. Sometimes H199/18 refers to the S-enantiomer of omeprazole, e.g. in the "Description" of Drug substance, Page 004-002-012 of original submission, Vol. 1.6. Sometimes it refers to "esomeprazole magnesium", e.g. cover letter to original submission.

In this review, "H199/18" refers to esomeprazole, while "esomeprazole magnesium" refers to the drug substance, esomeprazole magnesium trihydrate.

- 7. PHARMACOLOGICAL CATEGORY: proton pump inhibitor
- 8. <u>INDICATION:</u> acute healing of erosive esophagitis, maintenance of healing of erosive esophagitis, and treatment of symptomatic gastroesophageal reflux disease (sGERD)
- 9. **DOSAGE FORM:** delayed release pellets
- 10. STRENGTH: 20, and 40 mg. Approval only for 20 and 40 mg strengths

- 11. ROUTE OF ADMINISTRATION: oral
- 12. HOW DISPENSED: X RX OTC
- 13. CHEMICAL IDENTIFICATION:

N Bis (1H-Benzimidazole,5-methoxy-2-[(S)-[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl]-),magnesium salt, trihydrate

 $C_{34}H_{36}N_6O_6S_2Mg \times 3H_2O$

The molecular formula should be $(C_{17}H_{18}N_3O_3S)_2Mg \times 3H_2O$. See discussion under "Labeling" below

CAS Number 217087-09-7

MW= 767.2 g/mol (trihydrate) and 713.1 g/mol (anhydrous basis)

- 14. <u>SUPPORTING DOCUMENTS:</u> All are Type III. See Container Closure Section
- 15. RELATED DOCUMENTS NDA 19-810
- 16. CONSULTS: Biometrics Pending.
- 17. <u>REMARKS/COMMENTS</u>: There are a number of relatively minor issues. One major concern is the lack of testing for in the drug substance.
- 17. CONCLUSIONS & RECOMMENDATIONS: Approvable. The applicant should be sent a Discipline Review Letter.

Arthur B. Shaw, Ph.D.

Review Chemist HFD-180

APPEARS THIS WAY

Liang Zhou, Ph.D.

Chemistry Team Leader, HFD-180

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

NDA #: 21-154

CHEMISTRY REVIEW #: 1

DATE REVIEWED: 03-OCT-2000

SUBMISSION:

DOCUMENT DATE:

CDER DATE:

ASSIGNED DATE:

Original

28-FEB-2000

29-FEB-2000

01-MAR-2000

NAME & ADDRESS OF SPONSOR:

AstraZeneca LP

725 Chesterbrook Blvd. Wayne, PA 19087-5677

REPRESENTATIVE:

Gary P. Horowitz, Ph.D.

Executive Director, Regulatory Affairs

DRUG PRODUCT NAME:

Proprietary: Nexium™

Nonproprietary: esomeprazole magnesium

Code Name/#: H-199/18

PHARMACOLOLOGICAL CATEGORY: Antiulcerative

INDICATION: Eradication of *Helicobacter Pylori*

DOSAGE FORM/STRENGTH: Delayed release capsules, 20 and 40 mg.

ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:

Bis-(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole-1-yl) magnesium trihydrate

Mol. Formula: C₃₄H₃₆N₆O₆S₂Mg · 3 H₂O Mol. Weight: 767.2 CAS: 217087-09-7

| SUPPORTING DOCUMENTS: | IND |
|-----------------------|-----------------------|
| | NDA 19-810 and 21-153 |
| | DMF — |
| | |

RELATED DOCUMENTS:

REMARKS/COMMENTS: Nexium[™] (esomeprazole) Delayed Release Capsules was originally submitted to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) for the treatment of gastric esophageal reflux disease (GERD) on December 3, 1999. Subsequently, it was submitted to this Division on February 28, 2000 for eradication of *Helicobacter pylori* infections in conjunction with amoxicillin and clarithromycin in patients with duodenal ulcer disease or a history thereof.

NDA 21-154 incorporates by reference all Chemistry, Manufacturing and Controls information contained in NDA 21-153. Accordingly, CMC information is found in the chemist' review(s) of NDA 21-153 and is incorporated in this review by cross-reference. Summarized information is included here as a convenient reference. A copy of the list of chemistry deficiencies and comments is also included in this review.

DGCDP has taken an Approvable action on NDA 21-153 in part due to the CMC issues noted. The division also found the data did not support the companies claim of superiority to omeprazole.

CONCLUSIONS & RECOMMENDATIONS: Approvable. The HFD-180 chemistry team has sent a Discipline Review Letter to the sponsor.

Gene W. Holbert, Ph.D., Review Chemist

Concurrence:

HFD-590: N. Schmuff

15/12/1/00

cc:

Original: NDA 21-154

HFD-590: N. Schmuff HFD-590: Micro HFD-590: J. Meyer HFD-590: G. Holbert

HFD-590: S. Hundley

HFD-590: J. Fritsch

HFD-590: Biopharm File:

DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS

Review of Chemistry, Manufacturing and Controls

NDA #: 21-154

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 15-DEC-2000

SUBMISSION:

DOCUMENT DATE:

CDER DATE:

ASSIGNED DATE:

Original

28-FEB-2000

29-FEB-2000

01-MAR-2000

NAME & ADDRESS OF SPONSOR:

AstraZeneca LP

725 Chesterbrook Blvd. Wayne, PA 19087-5677

REPRESENTATIVE:

Gary P. Horowitz, Ph.D.

Executive Director, Regulatory Affairs

DRUG PRODUCT NAME:

Proprietary: Nexium™

Nonproprietary: esomeprazole magnesium

Code Name/#: H-199/18

PHARMACOLOLOGICAL CATEGORY: Antiulcerative

INDICATION: Eradication of *Helicobacter Pylori*

DOSAGE FORM/STRENGTH: Delayed release capsules, 20 and 40 mg.

ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME/STRUCTURAL FORMULA:

Bis-(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1-yl) magnesium trihydrate

Mol. Formula: C₃₄H₃₆N₆O₆S₂Mg · 3 H₂O Mol. Weight: 767.2 CAS: 217087-09-7

| SUPPORTING DOCUMENTS: | IND |
|-----------------------|-----------------------|
| | NDA 19-810 and 21-153 |
| | DMF — |
| | |

RELATED DOCUMENTS:

REMARKS/COMMENTS: AstraZeneca has responded to the Discipline Review Letter sent by the HFD-180 chemistry team. Their response has been reviewed and found acceptable (Arthur B. Shaw, NDA 21-153 Chemistry Reviews Nos. 2 and 3, dated 18 October and 06 December-2000, respectively). The chemistry reviewer states that the application may be approved from a CMC perspective.

CONCLUSIONS & RECOMMENDATIONS: This NDA may be approved with respect to CMC.

Gene W. Holbert, Ph.D., Review Chemis

Concurrence:

HFD-590: N. Schmuff

15/ 12/15/00

cc:

Original: NDA 21-154 HFD-590: N. Schmuff HFD-590: Micro HFD-590: J. Meyer HFD-590: G. Holbert HFD-590: S. Hundley HFD-590: J. Fritsch

HFD-590: Biopharm

File:

APPEARS THIS WAY ON ORIGINAL